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(54) Title: STABILE COMPOSITIONS COMPRISING LEVOSIMENDAN AND ALGINIC ACID

(57) Abstract

The present invention relates to pharmaceutical compositions of levosimendan comprising alginic acid for improving the stability of levosimendan in the compositions. Levosimendan is useful in the treatment of congestive heart failure.

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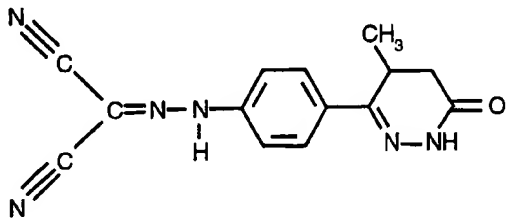
STABILE COMPOSITIONS COMPRISING LEVOSIMENDAN AND ALGINIC ACID

Technical field

The present invention relates to pharmaceutical compositions, particularly for oral administration, with improved stability comprising levosimendan, the (-) enantiomer of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-hydrazono]propanedinitrile, as the active ingredient. Levosimendan is useful in the treatment of congestive heart failure.

Background of the invention

Levosimendan, which is the (-)-enantiomer of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile, and the method for its preparation is described in EP 565546 B1. Levosimendan is potent in the treatment of heart failure and has significant calcium dependent binding to troponin. Levosimendan is represented by the formula:



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The hemodynamic effects of levosimendan in man are described in Sundberg, S. et al., Am. J. Cardiol., 1995; 75: 1061-1066. Pharmacokinetics of levosimendan in man after i.v. and oral dosing is described in Sandell, E.-P. et al., J. Cardiovasc. Pharmacol., 26(Suppl.1), S57-S62, 1995. The use of levosimendan in the treatment of myocardial ischemia is described in WO 93/21921. Clinical studies have confirmed the beneficial effects of levosimendan in heart failure patients.

The preparation of pharmaceutical compositions of levosimendan, particularly for oral use, has proved to be difficult. When combined with conventional excipients levosimendan shows poor stability and easily degrades under storage conditions. Therefore, there is a need for pharmaceutical preparations of levosimendan which show improved stability of the active ingredient under storage.

Summary of the invention

It has now been unexpectedly found that alginic acid significantly improves the stability of levosimendan in pharmaceutical compositions.

Thus the present invention provides a pharmaceutical composition of levosimendan, particularly for oral administration, with improved stability comprising alginic acid as a stability improving agent.

Detailed description

The compositions of the invention comprise generally about 0.1 - 99 % of alginic acid per weight of the composition. More typically, a composition of the invention comprises about 5 - 70 %, preferably about 10 - 40 %, of alginic acid per weight of the composition.

Typically, the composition of the invention is for oral administration. Such compositions include solid compositions in the form of e.g. tablets, dragees, capsules, powders and granules. The contents of the active compound in the composition of the invention is generally from about 0.01 to 100 %, preferably from 0.1 to 20 %, most preferably from 0.5 to 10 % per weight. In general levosimendan is administered orally to man in doses from about 0.1 to 10 mg, preferably from 0.5 to 5 mg once or several times a day depending on the age, body weight and condition of the patient.

In addition to levosimendan and alginic acid the composition of the invention may comprise pharmaceutically acceptable carriers and excipients. Pharmaceutically acceptable carriers and excipients include those which are used according to standard pharmaceutical practice and which are compatible with the active ingredient. For oral administration in tablet form, suitable carriers and excipients include microcrystalline cellulose such as Avicel PH101, lactose, corn starch, magnesium stearate, stearic acid, calcium phosphate and talc. For oral administration in capsule form, useful carriers and excipients include micro-crystalline cellulose, lactose, corn starch, magnesium stearate, stearic acid and talc. Capsules can be prepared by mixing the active ingredient with the carriers and excipients and placing the powdery mixture in capsules, e.g. hard gelatine capsules. Tablets can be prepared by mixing the active ingredient with the carriers and excipients and compressing the powdery mixture into tablets.

The composition may be designed to release the active ingredient rapidly or in a controlled/extended fashion. Typically long-acting compositions are prepared by mixing

the drug, a release controlling agent and possible excipients, and pressing the mixture into matrix tablets, or by coating a core of active ingredient with a release controlling coating so as to obtain coated tablets or granules. Typical release controlling agents include hydrophilic gel forming polymers such as hydroxypropylmethyl cellulose, which is commercially available in various types, e.g. Methocel K100LV (m.w. 26,000 g/mol), Methocel K4M (m.w. 86,000 g/mol, Methocel K15M (m.w. 120,000 g/mol) and Methocel K100M. The viscosity of these grades in 2 % water solution (20 °C) is 100 cP, 4000 cP, 15000 cP and 100000 cP, respectively.

The following examples are meant to further illustrate the invention without limitation.

EXAMPLE 1. The stability of formulations of the invention (1 and 2) and reference formulations (1 - 4) are compared in storage conditions.

Formulation 1 (hard gelatine capsule):

Levosimendan	2 mg
Methocel K100LV	46 mg
Alginic acid	23 mg
Avicel PH101	69.5 mg
Stearic acid	1.5 mg

Formulation 2 (pressed tablet):
Levosimendan : alginic acid 1:10

Reference formulation 1 (hard gelatine capsule):

Levosimendan	2 mg
Methocel K4M	35 mg
Avicel PH101	101.6 mg
Stearic acid	1.4 mg

Reference formulation 2 (hard gelatine capsule):

Levosimendan	2 mg
Lactose	197 mg
Magnesium stearate	1 mg

Reference formulation 3 (pressed tablet):
Levosimendan : lactose 1:100

Reference formulation 4 (pressed tablet):

Levosimendan : magnesium stearate 1:1

Formulation 1, consisting of a granule portion and a powder portion, was prepared by mixing Methocel K100LV, alginic acid and levosimendan (1 mg) until homogenous in a suitable mixer such as Turbula mixer or Zanchetta container mixer. The mass was dry

granulated by slugging (compressed using a tabletting machine). The compacted mass was sieved and granules of 0.7 – 1.7 mm were collected. For the powder portion, Avicel PH101 and levosimendan (1 mg) was sieved and mixed until homogenous in a suitable mixer such as Turbula mixer or Zanchetta container mixer. The granule portion and the powder portion and the stearic acid were mixed until homogenous in a suitable mixer such as Turbula mixer or Zanchetta container mixer. The mass was filled into hard gelatine capsules no 3.

In Reference formulations 1 and 2 the material was in a powder form. These formulations were prepared by mixing the components until homogenous in a suitable mixer such as Turbula mixer or Zanchetta container mixer. The mass was then filled into hard gelatine capsules no 3.

Formulation 2 and Reference formulations 3 and 4 were prepared by mixing the components until homogenous in a suitable mixer such as Turbula mixer or Zanchetta container mixer. The mixture was then pressed into tablets using a conventional tabletting machine.

The stability of the formulations in storage conditions was assessed by determining the level of degradation products of levosimendan in the formulations after storage. The results are given in Table 1.

Table 1. The presence of levosimendan degradation products (OR-1420 and OR-1368) in formulations of the invention (1 - 2) and in reference formulations (1 - 4) after storage. Rh = relative humidity.

	Storage conditions	OR-1420 formed	OR-1368 formed	Number of unknown degradation products
Formulation 1:	9 months 2 - 8 °C	0	0	0
Formulation 2:	8 months 25°C, rh 60%	0	0	0
Ref. formulation 1:	9 months 2 - 8 °C	0.25 %	0.25 %	1, 0.05 %
Ref. formulation 2:	3 months 25°C, rh 60%	1.32 %	0.07 %	5, 0.54 %
Ref. formulation 3:	3 months 25°C, rh 60%	0.75 %	0.23 %	10, 0.93 %
Ref. formulation 4:	7 weeks 25 °C	0	0	1, 1.0 %

Table 1 shows that alginic acid significantly improved the stability of levosimendan formulations in storage conditions as demonstrated by the absence of any degradation products of levosimendan after 8 - 9 months of storage. In contrast, the reference formulations containing no alginic acid show significant formation of levosimendan degradation products.

CLAIMS

1. A pharmaceutical composition comprising levosimendan as an active ingredient and alginic acid as a stability improving agent.

2. A composition of claim 1 wherein the amount of alginic acid is 0.1 - 99 % per weight of the composition.

3. A composition of claim 2 wherein the amount of alginic acid is 5 - 70 %, preferably 10 - 40 %, per weight of the composition.

4. A composition of any of claims 1 - 3, wherein the composition is for oral administration.

5. A composition of claim 4, which is in the form of tablets, dragees, capsules, powders or granules.

6. A composition of any of claims 1 - 5, wherein the amount of the active ingredient in the composition is from 0.1 to 20 % per weight of the composition.

7. A composition of any of claims 1-6 wherein the amount of the active ingredient is 0.1 to 10 mg.

INTERNATIONAL SEARCH REPORT

Int ational Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/50 A61K47/36 A61K9/16 A61K9/20 A61K9/28
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 92 12135 A (ORION YHTYMAE OY) 23 July 1992 see page 5, line 12-16 & EP 0 565 546 A cited in the application	1-7
Y	EP 0 091 767 A (MERCK SHARP & DOHME) 19 October 1983 see abstract	1-7
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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